FLNA gene

filamin A

Normal Function

The *FLNA* gene provides instructions for producing the protein filamin A, which helps build cells' extensive internal network of protein filaments called the cytoskeleton. The cytoskeleton gives structure to cells and allows them the flexibility to change shape. Filamin A primarily attaches (binds) to another protein called actin and helps it form the branching network of filaments that make up the cytoskeleton. Filamin A can also bind to many other proteins in the cell to carry out various functions, including the attachment of cells to one another (cell adhesion), cell movement (migration), determination of cell shape, and cell survival. These numerous functions involving filamin A have been found to play roles in regulating skeletal and brain development, the formation of heart tissue and blood vessels, and blood clotting.

Filamin A is also involved in the organization of the extracellular matrix, which is the lattice of proteins and other molecules outside the cell. Filamin A binds to proteins called integrins, which span the cell membrane and anchor cells to the extracellular matrix. Through this binding, cells are correctly positioned and signals can be exchanged between the cell and the extracellular matrix.

Health Conditions Related to Genetic Changes

FG syndrome

frontometaphyseal dysplasia

More than 10 mutations in regions of the *FLNA* gene called exons 4, 22, 29, 33, and 44 through 46 have been identified in people with frontometaphyseal dysplasia. This condition involves abnormalities in skeletal development and other health problems, including kidney, heart, and lung defects. The *FLNA* gene mutations that cause frontometaphyseal dysplasia are described as "gain-of-function" because they appear to enhance the activity of the filamin A protein or give the protein a new, atypical function. Different mutations in the *FLNA* gene appear to produce specific changes in the protein, resulting in particular signs and symptoms that are classified as individual *FLNA*-related disorders. Researchers believe that the mutations involved in frontometaphyseal dysplasia may change the way the filamin A protein helps regulate processes involved in skeletal development, but it is not known how changes in the protein relate to the specific signs and symptoms of the condition.

intestinal pseudo-obstruction

Intestinal pseudo-obstruction, a condition characterized by impairment of the muscle contractions that move food through the digestive tract (peristalsis), can be caused by mutations in the *FLNA* gene.

Some individuals with intestinal pseudo-obstruction have *FLNA* gene mutations that result in an abnormally short filamin A protein. Others have duplications or deletions of genetic material in the *FLNA* gene. Researchers believe that these genetic changes may impair the function of the filamin A protein, causing abnormalities in the cytoskeleton of nerve cells (neurons) in the gastrointestinal tract. These abnormalities result in impaired peristalsis, which causes abdominal pain and the other gastrointestinal symptoms of intestinal pseudo-obstruction.

Deletions or duplications of genetic material that affect the *FLNA* gene can also include nearby genes on the X chromosome. Changes in these additional genes may account for some of the other signs and symptoms, such as neurological abnormalities and unusual facial features, that occur in some affected individuals.

Melnick-Needles syndrome

At least seven mutations in a region of the *FLNA* gene called exon 22 have been identified in people with Melnick-Needles syndrome. This condition involves abnormalities in skeletal development and other health problems. The *FLNA* gene mutations associated with Melnick-Needles syndrome are described as "gain-of-function" because they appear to enhance the activity of the filamin A protein or give the protein a new, atypical function. Researchers believe that the mutations involved in Melnick-Needles syndrome may change the way the filamin A protein helps regulate processes involved in skeletal development, but it is not known how changes in the protein relate to the specific signs and symptoms of the condition.

otopalatodigital syndrome type 1

A small number of mutations in regions of the *FLNA* gene called exons 3, 4, and 5 have been identified in people with otopalatodigital syndrome type 1. This condition primarily involves abnormalities in skeletal development. The *FLNA* gene mutations that cause otopalatodigital syndrome type 1 all result in changes to the filamin A protein in the region that binds to actin. The mutations responsible for otopalatodigital syndrome type 1 are described as "gain-of-function" because they appear to enhance the activity of the filamin A protein or give the protein a new, atypical function. Researchers believe that the mutations involved in otopalatodigital syndrome type 1 may change the way the filamin A protein helps regulate processes involved in skeletal development, but it is not known how changes in the protein relate to the specific signs and symptoms of the condition.

otopalatodigital syndrome type 2

A small number of mutations in regions of the *FLNA* gene called exons 3, 4, and 5 have been identified in people with otopalatodigital syndrome type 2. This condition involves abnormalities in skeletal development and other health problems. Similar but more severe symptoms have been associated with mutations in exons 11 and 29. The mutations in exons 3, 4, and 5 result in changes to the filamin A protein in the region that binds to actin. The mutations responsible for otopalatodigital syndrome type 2 are described as "gain-of-function" because they appear to enhance the activity of the filamin A protein or give the protein a new, atypical function. Researchers believe that the mutations involved in otopalatodigital syndrome type 2 may change the way the filamin A protein helps regulate processes involved in skeletal development, but it is not known how changes in the protein relate to the specific signs and symptoms of the condition.

periventricular heterotopia

More than 120 *FLNA* gene mutations have been identified in individuals with periventricular heterotopia, a condition in which nerve cells (neurons) do not move (migrate) properly during the early development of the fetal brain leading to seizures and other neurological problems. Most of these mutations result in a protein that is too short and cannot perform its function, which makes the cytoskeleton disorganized and impairs cell movement. Neurons that do not migrate properly during development form clumps around the fluid-filled cavities (ventricles) near the center of the brain, resulting in the signs and symptoms of periventricular heterotopia.

In some cases, mutations result in the substitution of one protein building block (amino acid) for another amino acid in the protein sequence. These mutations may result in the production of a partially functional protein, causing a milder form of the disorder.

X-linked cardiac valvular dysplasia

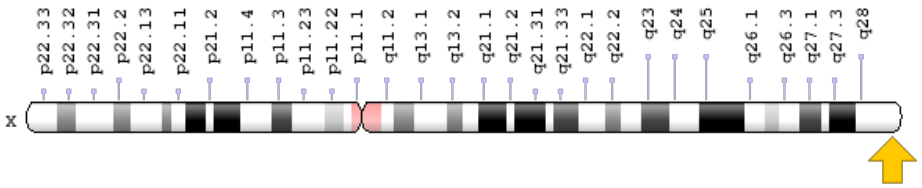
At least four mutations in the *FLNA* gene have been found to cause X-linked cardiac valvular dysplasia, a condition characterized by abnormally thick heart valves. Most of these mutations change single protein building blocks in the filamin A protein. These mutations likely alter the shape of the protein, impairing its ability to bind to actin and other proteins. As a result, the cell cytoskeleton is weakened and valve cells as well as the extracellular matrix are disorganized. The cells are not positioned properly within the valve, so the valve becomes malformed. In addition, the cells' decreased ability to change shape impairs the valves' ability to open and close when the heart pumps blood. It appears that excess proteins are produced in the abnormal extracellular matrix, causing the valves to become thickened and further impairing their ability to open and close normally.

It is unclear why the heart valves are the only tissue affected by these *FLNA* gene mutations. The mutations that cause X-linked cardiac valvular dysplasia occur in a different part of the gene than those that cause other disorders (described above). It has been suggested that the region of the filamin A protein affected by these mutations is necessary for binding to other proteins that play a significant role in heart development.

Chromosomal Location

Cytogenetic Location: Xq28, which is the long (q) arm of the X chromosome at position 28

Molecular Location: base pairs 154,348,529 to 154,374,638 on the X chromosome (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- ABP-280
- ABPX
- actin-binding protein 280
- DKFZp434P031
- filamin 1
- filamin A, alpha
- filamin A, alpha (actin binding protein 280)
- FLN
- FLN1
- FLNA_HUMAN

Additional Information & Resources

Educational Resources

- The Cell: A Molecular Approach (second edition, 2000): Organization of Actin Filaments
  https://www.ncbi.nlm.nih.gov/books/NBK9908/#A1771

GeneReviews

- FLNA-Related Periventricular Nodular Heterotopia
  https://www.ncbi.nlm.nih.gov/books/NBK1213
- Otopalatodigital Spectrum Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK1393

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28FLNA%5BTIAB%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- FILAMIN A
  http://omim.org/entry/300017

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_FLNA.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=FLNA%5Bgene%5D
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=3754
- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/2316
- UniProt
  http://www.uniprot.org/uniprot/P21333

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